Correlation between Neutrophil/Lymphocyte Ratio (NLR), lipid profile, lesion location and vascular cognitive impairment in acute ischemic stroke patients

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Abstract

Background: Stroke is the leading cause of long-term disability with significant clinical and socioeconomic impact worldwide. Hyperlipidemia and inflammation play major roles in ischemic stroke. This research focuses on the correlation of three factors, namely Neutrophil-Lymphocyte Ratio (NLR), lipid profile, and lesion location, with vascular cognitive impairment (VCI). These factors may serve as potential predictors for VCI.
Purpose: This research aims to study the correlation between NLR, lipid profile, and lesion location with vascular cognitive impairment. In addition, this research aims to explore those potential biomarkers as predictors of vascular cognitive impairment.
Methods: This was a cross-sectional study which included 107 patients diagnosed with ischemic stroke from February 2022 to January 2023 with a history of admission to the hospital within 72 hours. After they signed an informed consent form, every patient had history taking, physical exam, lipid profile, routine blood test, Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment Indonesian Version (MoCA-Ina) on the first hospital day. Statistical tests were done with Spearman correlation method.
Results: The data distribution was not normal for INR and MoCA-INA values ($p<0.05$). Total cholesterol was insignificantly ($p=0.092$) correlated with MoCA-INA score with low correlation value ($r=-0.293$). HDL was significantly ($p=0.035$) correlated with MoCA-INA score with moderate correlation value ($r=0.461$). LDL was significantly ($p=0.028$) correlated with MoCA-INA score with low correlation value ($r=-0.387$). Triglycerides was insignificantly ($p=0.440$) correlated with MoCA-INA score with very weak correlation value ($r=-0.137$). NLR was significantly ($p=0.015$) correlated with MoCA-INA score with moderate correlation value ($r=-0.412$).
Conclusions: Lipid profile is correlated with cognitive impairment in post-stroke patients, with HDL being a protective factor, and LDL as risk factor. NLR was associated with worse cognitive function and LDL was directly proportional to NLR. Lesion location reporting was highly heterogeneous and more uniformed reporting is recommended for future research.

Keywords: cognitive; HDL; LDL; location; NLR; stroke

Introduction

Globally, stroke remains a prominent cause of disability and death, especially in developing countries. This is also true for Asian countries, in which hypertension, followed by diabetes mellitus and smoking are the

most common risk factors (Venketasubramanian et al., 2017). These disabilities are preventable with prompt treatment which focuses on rapid reperfusion by thrombolysis and thrombectomy. There are also recent advancements in research regarding biomarkers that may predict the incidence of these disabilities (Campbell et al., 2019). Healthcare settings in low-income and middle-income countries (LMICs), such as Indonesia, present unique challenges regarding prompt stroke treatment. These challenges, of which funding is particularly stark, have contributed to the burden of disease in LMICs such as Indonesia (Gadama et al., 2017; Pandian et al., 2020).This might indicate the reason why Indonesia has the highest age and sex-standardized mortality (193.3/100,000) and disability-adjusted life years lost (3,382.2/100,000) in South East Asia (Venketasubramanian et al., 2022).

Stroke-related disability is not confined to just physical impairments, but also those that are psychiatric in nature. Cerebrovascular diseases such as ischemic stroke are a major cause of cognitive impairment following the years post-stroke, in which 10% develop after the initial stroke, and 30% develop at the end of one year. With vascular dementia being a major cause of dementia, second only to Alzheimer's disease, an understanding of its risk factors proves to be a crucial research objective (Chohan et al., 2019). Having said that, it is noteworthy that not all post-stroke cognitive impairment fulfill the diagnostic criteria for dementia, making vascular cognitive impairment (VCI) a more appropriate term (Lim et al., 2021). It is also important to differentiate between the overlap between Alzheimer's disease (AD) and VCI, of which one third of demented post-stroke patients can be attributed to AD (Vijayan & Reddy, 2016). This research focuses on the predictors of post-stroke VCI, which is not exclusive to vascular dementia.

This research focuses on the correlation of three factors, namely Neutrophil-Lymphocyte Ratio (NLR), lipid profile, and lesion location, with VCI. These factors may serve as potential predictors for VCI. NLR is a simple ratio between the neutrophil and lymphocyte count, in which an increase is present in conditions such as bacterial or fungal infection, myocardial infarction, severe trauma, cancer, atherosclerosis, and acute stroke (Buonacera et al., 2022). A meta-analysis has shown that an elevated NLR is significantly associated with a 1.1-1.3 fold increased risk of poor prognosis in stroke patients (W. Li et al., 2021). Another study further detailed on this, explaining that patients with cerebral small vessel disease (CSVD) with an increased NLR have an increased risk of VCI (Hou et al., 2022). Regarding lipid profile, previous studies have shown that LDL-C and HDL-C are risk factors for atherosclerosis and white matter abnormalities which may cause cognitive impairment, although the latter has shown mixed results (Appleton et al., 2017; Lysandra et al., 2020; Menet et al., 2018).The lesion location also greatly affects the development of post-stroke cognitive impairment (PSCI). A pooled analysis study showed that several brain regions, namely the left frontotemporal lobes, left thalamus, and right parietal lobe, were strongly associated with PSCI (Weaver et al., 2021). Based on these prior papers, this research aims to study the correlation between NLR, lipid profile, and lesion location with vascular cognitive impairment. Hence, these parameters can be explored as potential predictors for vascular cognitive impairment.

Materials and Methods

Participant Recruitment

Subjects who met the inclusion criteria signed an informed consent form and this was followed by history taking, physical examination, lipid profile routine blood test, Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment Indonesian Version (MoCA-Ina) on the first hospital day. Subjects were conscious and cooperative, and could read as well as write. This is a cross-sectional study which employed a total sampling approach. Bias was minimized by training enumerators to standardize the examinations done to each patient.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were all patients diagnosed with ischemic stroke with a history of admission to the hospital within 72 hours of onset and patients who agreed to participate in this study as evidenced by signing the informed consent statement by themselves or by a first-degree relative as stipulated in the research ethics protocol issued by Dr. Moewardi General Hospital Health Research Ethics Committee through ethical clearance number 208/II/HREC/2022 which was approved on 13 February 2022. This is in accordance with the WMA (World Medical Association) declaration of Helsinki.

The researchers excluded patients who had previous symptoms and signs related to neuro-behavioral disorders, aged ≥ 65 years, patients with transient ischemic attack (TIA), recurrent ischemic stroke, second stroke, hemorrhagic stroke, and had severe comorbidities (acute coronary syndrome, diabetes mellitus), hematological disorders (especially abnormalities in liver and kidney function tests), and neoplasms), patients with a history of smoking and alcohol consumption, patients with a previous history of inflammatory diseases such as rheumatoid arthritis and Systemic Lupus Erythematosus (SLE) or a history of steroid and immunomodulatory drugs) and patients with a history of admission to hospital over 72 hours post-onset.

Statistical Tests

Statistical tests in this study were carried out using the Spearman correlation method to determine the results of the correlation between total cholesterol,

Table 1. Descriptive Values and Results of Correlation Analysis between Involved Areas and NLR and MoCA-INA Values

Area	In-volve-ment	Total Popu-lation	NLR			MoCA-INA		
			Median (min; max)	Correla-tion	P-val-ue	Median (min; max)	Correla-tion	P-val-ue
Frontal Lobe	Yes	11	2.99 (1.89; 17.33)	-0.51	0.600	26.00 (16; 30)	-0.137	0.158
	No	96	3.44 (1.33; 37.84)			28.00 (5; 30)		
Parietal Lobe	Yes	12	3.51 (1.89; 9.68)	-0.001	0.992	28.00 (18; 30)	0.060	0.542
	No	95	3.28 (1.33; 37.84)			27.00 (5; 30)		
Occipital Lobe	Yes	2	4.57 (2.74; 6.39)	0.27	0.784	25.00 (23 ;27)	-0.088	0.368
	No	105	3.39 (1.33; 37.84)			27.00 (5; 30)		
Temporal Lobe	Yes	7	3.61 (1.89; 9.68)	0.047	0.634	24.00 (16; 30)	-0.130	0.183
	No	100	3.33 (1.33; 37.84)			27.00 (5; 30)		
Internal Capsule	Yes	56	3.33 (1.33; 37.84)	-0.006	0.953	27.00 (5; 30)	-0.116	0.234
	No	51	3.41 (1.58; 19.59)			28.00 (16; 30)		
Cortical Capsular	Yes	65	3.49 (1.33; 17.33)	0.52	0.594	27.00 (5; 30)	-0.135	0.164
	No	42	3.19 (1.58; 37.84)			28.00 (9; 30)		

Table 2. LDL and MoCA-INA Confusion Matrix

		Outcome (MoCA-INA): Cognitive Impairment		Total
		Moderate - Severe	Mild	
LDL	High risk	39	15	54
	Low risk	11	42	53
	Total	**50**	**57**	**107**

Table 3. NLR and MoCA-INA Confusion Matrix

		Outcome (MoCA-INA): Cognitive Impairment		Total
		Moderate - Severe	Mild	
NLR	High risk	43	10	53
	Low risk	8	46	54
	Total	**51**	**56**	**107**

Table 4. Correlation of lipid profile with NLR

Variable	r	p
Total Cholesterol – NLR	0.182	0.124
HDL – NLR	-0.354	0.376
LDL – NLR	0.489	0.058
Triglycerides – NLR	0.076	0.413

high density lipid (HDL), low density lipid (LDL), triglyceride, neutrophile lymphocyte ratio (NLR), and lesion location to the MoCA-INA score. In addition, statistical calculations on the effect of total cholesterol, HDL, LDL, and triglyceride on NLR also used Spearman correlation. The use of statistical tests with Spearman correlation was chosen because, based on the results of the calculation of data normality using the Kolmogorov-Smirnov test, abnormal data distribution results were obtained. The results of the Spearman correlation test will be expressed in the correlation coefficient (r) which will measure the strength and direction of the linear relationship between variables. Statistical analysis was done by a separate group that did not examine the patients so as to minimize bias.

Results

A total of 107 patients fulfilled the inclusion and

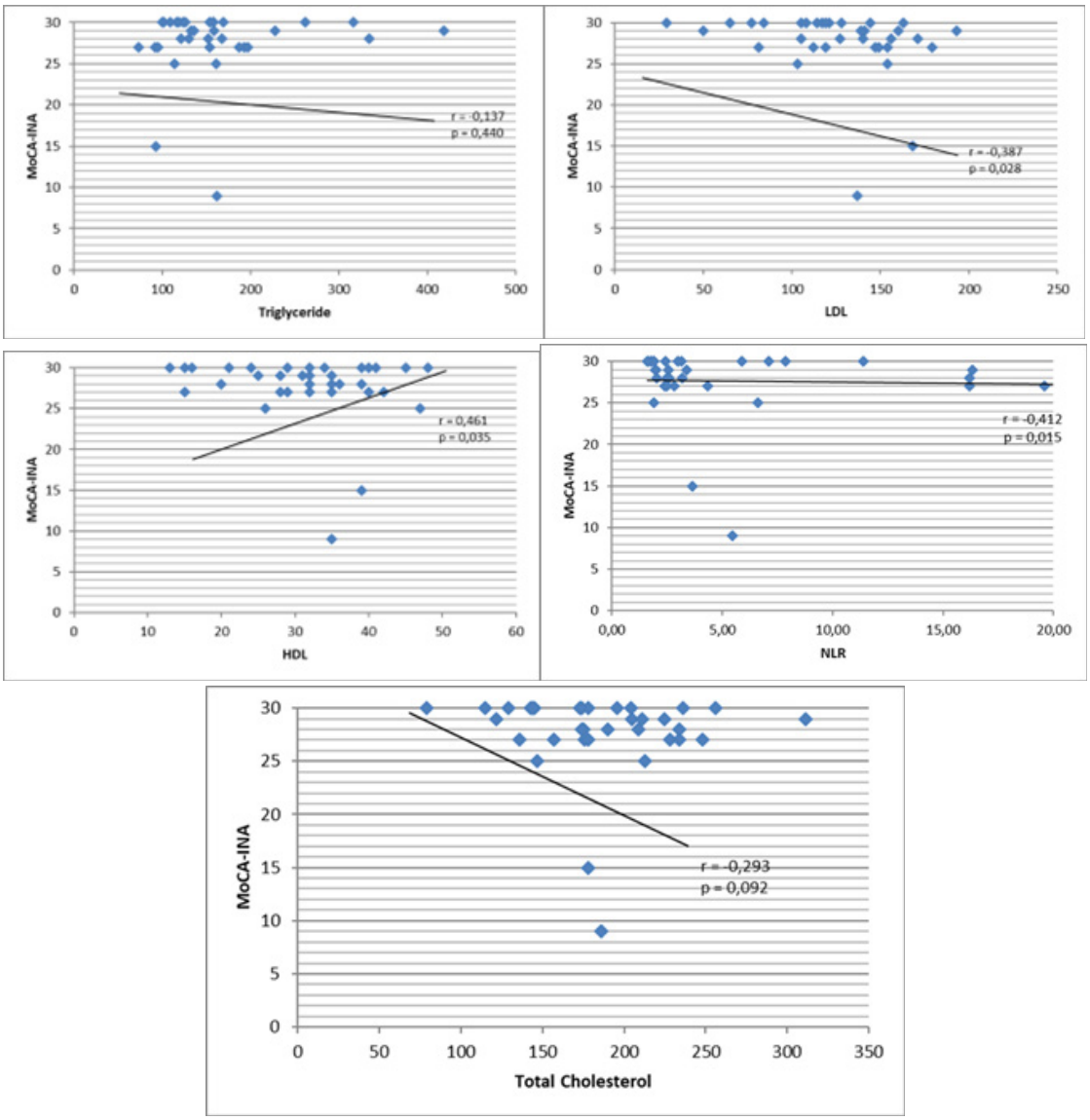

Figure 1. Correlation of total cholesterol, HDL, LDL, triglycerides, and NLR with MoCA-INA

exclusion criteria out of 948 acute ischemic stroke patients. They consisted of 62 men (57.9%) and 45 women (41.2%). The average age of the study subjects was 59.93 ± 9.55 years with an age range of 36 to 83 years. The highest number of research subjects was in the age group of 50-60 years, as many as 40 patients (37.4%). Meanwhile, the lowest number of study subjects was found in the age group between 80-90 years, totaling one person (0.9%). The NLR value of the total study subjects ranged from 1.33 - 37.84 with an average value of 5.01, while the value of the patient's MoCA-INA test ranged from 5 - 30 with an average value of 25.95, as shown in Table 1.

In the normality assessment using One-Sample Kolmogorov-Smirnov, it was found that the data distribution was not normal for INR and MoCA-INA values ($p<0.05$). The correlation assessment between lobe location and INR and MoCA-INA values was calculated using the Spearman correlation statistical method. Based on the statistical calculation results, it was found that the affected area did not give significant results on the NLR value and MoCA-INA score. However, the correlation assessment between the location of the affected area and the MoCA-INA score showed a generally negative trend except in the parietal lobe.

Based on the results of the correlation assessment between total cholesterol and MoCA-INA score (Figure 1.), it was found that an increase in total cholesterol had a negative correlation with the MoCA-INA score. This means that any increase in the total cholesterol value will cause a decrease in the MoCA-INA score. However, the correlation value of this assessment showed a low correlation value ($r = -0.293$) and insignificant results ($p = 0.092$).

Based on the results of the correlation assessment between HDL and MoCA-INA scores

(Figure 1.), it was found that an increase in HDL had a positive correlation with MoCA-INA scores. This means that any increase in HDL value will lead to an increase in MoCA-INA score. In assessing the correlation between HDL and MoCA-INA scores, the results were significant (p = 0.035) with a moderate correlation value (r = 0.461).

Based on the results of the correlation assessment between LDL and MoCA-INA scores (Figure 1.), it was found that an increase in LDL had a negative correlation with MoCA-INA scores. This means that any increase in LDL value will cause a decrease in MoCA-INA score. In assessing the correlation between LDL and MoCA-INA score, the results were significant (p = 0.028) with a low correlation value (r = -0.387).

Based on the results of the correlation assessment between triglycerides and MoCA-INA scores (Figure 1.), it was found that an increase in triglycerides had a negative correlation with MoCA-INA scores. This means that any increase in LDL values will lead to a decrease in MoCA-INA scores. In assessing the correlation of triglycerides with MoCA-INA scores, the results were not significant (p = 0.440) with a very weak correlation value (r = -0.137).

Based on the results of the correlation assessment between NLR and MoCA-INA score (Figure 1.), it was found that an increase in NLR has a negative correlation with the MoCA-INA score. This means that any increase in NLR value will lead to a decrease in MoCA-INA score. In assessing the correlation between NLR and MoCA-INA score, the results were significant (p = 0.015) with a moderate correlation value (r = -0.412).

Table 2 shows data on demographic differences between low-density lipoprotein (LDL) values and the MoCA-INA (Montreal Cognitive Assessment - Indonesia), which is a measurement tool to assess cognitive impairment. Cognitive impairment was divided into two categories, moderate-severe and mild. Meanwhile, LDL values were divided into two categories, namely high risk and low risk. From the table, there are demographic differences between LDL and MoCA-INA values. In general, high LDL values were associated with more severe cognitive impairment (72.2%) when compared to patients with low LDL values (20.75%). In its use as a predictor for worse cognitive events, LDL values had a sensitivity of 72.2%, specificity of 79.2% and accuracy of 75.7%.

Table 3 shows the correlation between NLR (neutrophil-to-lymphocyte ratio) values and MoCA-INA. From the table, there are differences in demographic data between NLR and MoCA-INA values. In general, high NLR values were associated with more severe cognitive impairment (81.1%), compared to low NLR (14.8%). In its use as a predictor for worse cognitive events, the NLR value had a sensitivity of 81.1%, specificity of 85.2% and accuracy of 83.2%.

Table 4 shows the correlation between lipid profiles (total cholesterol, HDL, LDL, and triglycerides) and NLR (neutrophil-to-lymphocyte ratio), which is an indicator of systemic inflammation. The r value indicates the magnitude of the relationship between two variables, while the p value indicates the statistical significance of the relationship. The Z value indicates the result of the difference test between the two correlations tested. From the table, only LDL has a moderately strong positive correlation with NLR (r = 0.489), but this relationship was not statistically significant (p = 0.058). This means that the higher the LDL value, the higher the NLR value, but this relationship cannot be confirmed because it may be due to other factors or coincidence. Total cholesterol, HDL, and triglycerides had no significant correlation with NLR (p > 0.05). The results of the difference test between the four correlations showed that there was no significant difference between the correlations of total cholesterol, HDL, LDL, and triglycerides with NLR values (Z = 0.7632, p > 0.05). This means that the four correlations have the same strength in explaining the relationship with NLR.

The results showed that there was no significant relationship between lipid profile and NLR, except for LDL which had a strong positive correlation but was not significant. This suggests that LDL may have an influence on systemic inflammation as measured by NLR, but this relationship needs to be further investigated using more accurate and sensitive methods. Total cholesterol, HDL, and triglycerides had no influence on NLR. In addition, there was no significant difference between the correlation of total cholesterol with NLR and the correlation of HDL with NLR.

Discussion

The Effect of Lipid Profile on Cognitive Function

Excessive low-density lipoproteins (LDL) have been shown to be involved in the narrowing of blood vessels, which may lead to ischemic stroke. Atherosclerosis, a chronic inflammatory disease characterized by serum lipid metabolism disorder and excessive cholesterol loading macrophages in the blood vessel wall, is the main cause of cerebrovascular diseases, including stroke (Li, J., et al., 2021). High concentrations of LDL cholesterol have been shown to increase the risk of ischemic stroke, while a reduction in LDL cholesterol levels has been associated with a decreased risk of ischemic stroke recurrence (Chen et al., 2020; Yuan et al., 2020). Furthermore, excess blood lipid levels, including LDL cholesterol, have been implicated in the initiation and progression of atherosclerosis, which can lead to a decrease in vessel diameter and elasticity, potentially impacting blood pressure and contributing to hypertension, ultimately leading to stroke (Austin et al., 2015).

The accumulation of LDL on the walls of blood vessels can cause hardening and narrowing of the

arteries, leading to atherosclerosis, which, in turn, can block blood flow and trigger stroke (Ali et al., 2022). Macrophage cholesterol accumulation, a critical process in the development of atherosclerotic plaques, is considered a significant factor in heart attacks and strokes (Zhao et al., 2006). Additionally, carotid atherosclerosis has been identified as a major risk factor for stroke, even in the absence of advanced stenosis, highlighting the role of atherosclerosis in stroke risk (Daher et al., 2014; Liu et al., 2017).

The narrowing of blood vessels can significantly reduce brain oxygen levels, leading to adverse effects on brain function and health. Hypertensive disorders, such as hypertension, can promote stroke through increased shear stress, endothelial dysfunction, and large artery stiffness, which can transmit pulsatile flow to the cerebral microcirculation, ultimately impacting oxygen delivery to the brain (Cipolla et al., 2018). Additionally, hypercholesterolemia and immune mechanisms have been implicated in the pathogenesis of atherosclerosis, which can lead to the narrowing of blood vessels and subsequently reduce oxygen supply to the brain. Cerebral small vessel disease, a condition associated with stroke, can manifest as a reduction in brain oxygen levels due to compromised blood supply resulting from vessel abnormalities (Li et al., 2018). Acute ischemic stroke, characterized by decreased blood supply to the brain, leads to reduced oxygen supply and subsequent damage to brain tissue (Rahma et al., 2022). Furthermore, variations in blood oxygenation values have been reported in the presence of pathology, including brain ischemia, highlighting the impact on brain oxygen levels (Christen et al., 2012).

Excessive long-term inflammation of the blood vessel wall may lead to increased endothelial cell permeability and enhanced rates of lipid entry, exacerbating the development of atherosclerosis, which can contribute to reduced brain oxygen levels (Meng et al., 2020). The dramatic stiffening of blood vessels and the effective reduction in diameter can increase the risk of vessel blockage or rupture, leading to ischemic events such as stroke and impacting brain oxygenation (Browning et al., 2018). Small blood vessels within the brain are particularly vulnerable to damage due to high pressure and pulsatile flow, which can compromise oxygen delivery to the brain (Pase et al., 2016). Additionally, the accumulation of lipids in blood vessels can affect blood flow and oxygenation, potentially impacting brain oxygen levels (Wang et al., 2020).

The Effect of NLR on Cognitive Function

Numerous studies have shown that an elevated neutrophil lymphocyte ratio is associated with an increased risk of cognitive decline in various populations (Iyigundogdu et al., 2021). These findings suggest that the inflammatory response, represented by the neutrophil lymphocyte ratio, plays a crucial role in cognitive function and decline. Additionally, the neutrophil lymphocyte ratio has been proposed as a potential biomarker for predicting cognitive decline in post-stroke patients (Cunningham & Hennessy, 2015; Fest et al., 2019). Furthermore, studies have demonstrated that an elevated neutrophil lymphocyte ratio is associated with increased stroke severity, poorer functional outcomes, and higher mortality rates in post-stroke patients, further highlighting the potential importance of this marker in assessing cognitive function and overall prognosis (Chong et al., 2021; Ramos-Cejudo et al., 2021; Wan et al., 2020).

The Correlation between Lipid Profile and NLR

In addition to the impact of lipid profiles on cognitive function, recent research has also explored the association between lipid profile and neutrophil lymphocyte ratio in post-stroke patients (Angkananard et al., 2018; Tok et al., 2014; Wan et al., 2020; Xue et al., 2017). Neutrophil lymphocyte ratio is a marker of systemic inflammation and immune response. It is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and has been suggested as a potential indicator of inflammation and immune activation in various health conditions (Yu et al., 2023; Zhu et al., 2018; Zuo et al., 2019). Some studies have found a positive correlation between lipid profile and neutrophil lymphocyte ratio in post-stroke patients. These findings suggest that dyslipidemia may not only contribute to cognitive impairment but also promote systemic inflammation, leading to an increase in neutrophil lymphocyte ratio.

Furthermore, studies have shown that elevated neutrophil lymphocyte ratio is associated with poorer cognitive function and increased risk of cognitive decline in various populations, including post-stroke patients (Huang et al., 2023; Leonardo & Fregni, 2023; Lin et al., 2018; McColl et al., 2007). However, it is important to note that the relationship between lipid profile, neutrophil lymphocyte ratio, and cognitive function is complex and multifactorial, and further research is needed to fully understand the underlying mechanisms and potential therapeutic implications (Bi et al., 2021; Gimeno et al., 2008; Wang et al., 2020). Moreover, the association between lipid profile and neutrophil lymphocyte ratio in post-stroke patients adds another layer of complexity to our understanding of the relationship between inflammation, lipid metabolism, and cognitive function. These findings suggest the potential role of lipid profile and neutrophil lymphocyte ratio as biomarkers for assessing cognitive function and inflammatory status in post-stroke patients (Iyigundogdu et al., 2021).

The Effect of Lesion Location on Cognitive Impairment

According to recent studies, several areas of the brain have been associated with post-stroke cognitive impairment. A study identified these areas to be the left angular gyrus, left basal ganglia

structures and the white matter around the left basal ganglia (Weaver et al., 2021). Another study identified the anterior thalamic radiation as a crucial area, where a lesion in that area would sever structural connections to the frontal lobe (Lim et al., 2021). Another study identified lesions in the temporal area, or involving multiple sites lead to a higher incidence of cognitive impairment (Utomo & Pinzon, 2023). These variance warrants for a more uniformed description of lesion location in the event of post-stroke cognitive impairment. This would allow a more homogenous data comparison between studies and determine lesion locations that would predict post-stroke cognitive impairment.

Conclusions

In conclusion, our study found that lipid profile is correlated to cognitive function in post-stroke patients, with HDL being a protective factor, and LDL a risk factor. We also found a higher NLR to be a reliable predictor of worse cognitive function. Regarding the correlation between lipid profile and NLR, we found that LDL is directly proportional to NLR, despite not being significant, whereas the other lipid parameters had no effect on NLR. The possible mechanisms underlying these findings have also been discussed, namely the deposition of lipid plaques in the blood vessels, which will, in turn, reduce cerebral perfusion. Regarding lesion location and its impact on cognitive impairment, future research needs to be more uniformed in reporting the areas involved to enable a more thorough analysis. This study is limited in explaining the causality of these factors as it is a cross-sectional study. Future cohort and case control studies are needed to determine the causality of these variables. In nursing practice, these findings may inform the use of lipid profile and NLR to potentially predict cognitive impairment in post stroke patients.

Declaration of Interest

All authors declare that they have no conflict of interests.

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Data Availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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